RotaTeq® and Kawasaki Disease Pre- and Post-Licensure Experience

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Overview

- Background on RotaTeq label change and pre-licensure cases
- FDA Label revision
- Kawasaki Disease (KD) epidemiology
- Post-licensure reports
  - Vaccine Adverse Event Reporting System (VAERS)
  - Vaccine Safety Datalink (VSD)
  - Merck Post-marketing Phase 4 Study
- Summary
- Conclusions

Background on RotaTeq® Label Change

- Original FDA approved label did not include KD cases
- KD cases original license application (4/05)
  - 3 vaccine : 0 placebo
- KD cases 4 month safety update (8/05)
  - 5 vaccine: 0 placebo
- Swiss regulatory agency inquiry, FDA review of KD cases (2/07)
  - 5 vaccine : 1 placebo

RotaTeq® Kawasaki Cases Pre-Licensure

AN	Rx	Race Sex Country	Age at KD (wks)	Dose	Days Post Dose	Concomitant vaccines at time of KD diagnosis	3 doses study vaccine completed
5402	Placebo	White Male (Finland)	14.2	1	16	None listed	no
39834	RotaTeq	Black Male (US)	13.9	1	27	DTaP, IPV, Hib, Prevnar	yes
97128	RotaTeq	Hispanic Male (US)	12.6	2	4	None listed at dose 2	yes
76738	RotaTeq	White Female (US)	20.4	2	2	Pediarix, Hib, Prevnar	yes
39855	RotaTeq	White Female (US)	22.3	3	30	DTaP, Hib, Prevnar, IPV	yes
94275	RotaTeq	Black Female (US)	20.1	3	16	Prevnar, IPV	yes

FDA Label Revision June 2007

- *Serious Adverse Events*

  Kawasaki Disease

  In the phase 3 clinical trials, infants were followed for up to 42 days of vaccine dose. Kawasaki disease was reported in 5 of 36,150 vaccine recipients and in 1 of 35, 536 placebo recipients with unadjusted relative risk 4.9 (95% CI 0.6, 239.1).

FDA Label Revision June 2007 (2)

- *Post-marketing reports*

  In post-marketing experience, the following adverse events have been reported in infants who have received RotaTeq:

  Infections and Infestations

  Kawasaki disease

- No change in **Indications**
- No change in **Warnings/Precautions**

Kawasaki Disease Epidemiology

- In the United States, leading cause of acquired heart disease in children (>4,000 children each year)
  - ~80% of patients aged < 5 years
- Incidence in children <5 years in the U.S. approximately 9 to 19 per 100,000 per year (Belay et al, PIDJ 2000)
- KS hospitalization weighted incidence rates from Kids' Inpatient Database (KID) 2003*
  - 21 per 100,000 per year (95% CI 18.3-24.1) in all infants
  - 11 per 100,000 per year (95% CI 8.7-13.3 in infants aged <6 months

* Ermias Belay, CDC's KS program, personal communication (unpublished), 20% of the "age in months" data missing, therefore, rates for children <6 months could be underestimated

Kawasaki Disease Epidemiology (2)

- Kawasaki disease has not been reported as associated with vaccinations
- In a 1983 JID article by Matsuno and Utagawa, authors reported the finding of either rotavirus particles and/or presumptive capsomers in 29 (74%) of 39 stools specimens obtained within a few days of admission to 3 Tokyo hospitals for KD
  - No confirmatory studies in the literature

Post-marketing Experience

- Vaccine Adverse Events Reporting System (VAERS)
- Vaccine Safety Datalink (VSD)
- Merck Post-marketing Study

Suspected Kawasaki Disease Reports in VAERS after Rotateq®

- 4 reports following RotaTeq® vaccination as of June 19, 2007
  - One received after FDA label revision
- ~ 6 million RotaTeq® doses distributed as of June 6, 2007*
- Reported rates within expected range
  - Subject to VAERS limitations
  - Providers may not associate KD and vaccines

* Merck, unpublished

Suspected Kawasaki Disease following RotaTeq® in VAERS*

Case #	Race Sex (State)	Age (months)	Dose	Interval (days)	Main Symptoms/signs	Treat-ment
1	Asian Female (HA)	2	1	0	Fever, rash, conjunctivitis. cracked lips	IVIG, aspirin
2	Black/ Hispanic (TX)	2	1	3	Rash, chapped red lips, conjunctival injection, edema of hands and feet, coronary ectasia	IVIG and aspirin
3	Female (NC)	61/2	3	0	Fever, rash, edema of hands and feet, Conjunctival injection	Unk
4	Male (CA)	5	2	14	Unk	Unk

* They all received multiple other childhood vaccinations on the same day, including DTaP, Hib, Hep B, Prevnar and IPV

Suspected Kawasaki Disease Reports for all Vaccines in VAERS*

- Ongoing overall VAERS review since 1990
- 81 suspected KD cases after all vaccinations identified as of June 20, 2007
- 44 of them reported from the U.S.
  - 19 were aged <1 year

** Wei Hua (FDA) personal communication, preliminary

Kawasaki Disease after RotaTeq® in CDC's Vaccine Safety Datalink (VSD) Study*

- Preliminary findings from 6 VSD sites
- One unconfirmed KD case ≤30 days post vaccination after 68,858 Rotateq doses as of June 17, 2007
  - Lower than expected
- VSD is incorporating KD into ongoing rapid cycle analysis of RotaTeq adverse events

*Source: Eric Weintraub, James Baggs, Paul Gargiullo, Edward Belongia and the VSD study group

Merck Observational Phase 4 Study Third Quarterly Report*

- Includes results from infants vaccinated with Rotateq and concurrent controls vaccinated during the first 3 quarters of 2006
- For the primary analysis window of 0-30 days after each dose:
  - No KD cases (or vasculitis) reported in either the Rotateq vaccines (n=7,196) or the concurrent controls (n=14,130)

*Source: Merck, unpublished

Summary
RotaTeq® and Kawasaki Disease

- Signal from pre-licensure clinical trials now captured in Label
- Kawasaki reports in VAERS within expected range, but cannot exclude risk
- Ongoing observational studies (VSD, Phase 4)
  - Data reassuring but limited by insufficient power

Conclusion, Future Activities

- At this time, no cause and effect relationship established between KD and RotaTeq or any other vaccine
- FDA, CDC and Merck continue to monitor safety of Rotateq vaccine using VAERS, VSD and Merck's Phase 4 data

- Backup slides

RotaTeq® Kawasaki Disease Cases Pre-Licensure

AN	Rx	Race Sex Ctry	Age in wks at KD	Dose	Days Post Dose	Findings	IVIG & ASA
5402	Plac	White Male Finland	14.2	1	16	Fever x 5 days, rash, palmar erythema, red lips, swollen feet, red BDG scar normal echo days 5, 12, 13, relapse day 13	Yes, twice
39834	Rota -Teq	Black Male US	13.9	1	27	Fever x 4 days, bulbar injection, palmar erythema, red truncal rash, chapped and bleeding red lips, wide coronary arteries on echo day 4 , echo improved on day 12	Yes
97128	Rota -Teq	Hispan Male US	12.6	2	4	Fever ? duration, conjunctivitis, UTI, Echo with mild coarc, Patent foramen ovale, fine coronaries day 4 and repeat echo WNL day 33	ASA
76738	Rota -Teq	White Female US	20.4	2	2	Fever x 3 days, red lips, puffiness, conjunctival injecton, lacy rash, Echo neg day 3 doing well 2 wks. post disccharge	Yes
39855	Rota -Teq	White Female US	22.3	3	30	Fever x 5 days, rash conjunctivitis, strawberry tongue, irritable, dilated coronary artery day 4 and day 17 Echo WNL 5 months later	Yes
94275	Rota -Teq	Black Female US	20.1	3	16	Fever ? Duration, rash, palmar erthema, desquamation, relapse at day 32 Echo coronary artery dilatation, pericardial effusion days 7 and 17, Echo WNL day 19 and WNL 4 months after SX onset	Yes

Pre-licensure Placebo KD Case AN 05402

- 12 week old white male, Finland, No concomitant vaccines listed
- Day 16 post dose 1
  - Fever, irritability
- Day 18 post dose 1
  - lethargy, pale, tender stomach, right ileocecal mass, abd U/S & lower GI WNL, Rx Ceftriaxone and Flagyl, stool neg rotavirus, blood and CSF cultures neg
- Day 20 post dose 1
  - Rash, swollen feet/palms, peeling fingertips, erythematous lips, "red" BCG scar
  - "Kawasaki-like" vasculitis suspected
- Day 21 post dose 1
  - 5th day of fever, irritable , CRP rising, repeat CSF and blood cultures neg
  - Rx IVIG (2 g/kg rec'd 12.3 g over 3 days and ASA 70mg/kg in 3 doses) normal Echo, CRP 235.5 mg/L discontinued study
- Day 25 discharged home
- Day 28 post dose 1
  - Re-hospitalized tired, swollen feet, red lips, peeling fingertips, elevated temp
  - Rx IVIG 7.2 g/day x 2 days and ASA 150 mg over 3 days then 25 mg qd x 3 mos.
  - Echo coronaries a bit enlarged but WNL
- Discharged Day 32 post dose 1 on ASA
- Day 39 post dose 1
  - To ER for swollen feet, normal exam, thrombocytosis, continues on ASA
- Day 91 post dose 1
  - normal exam and ASA therapy completed

Pre-licensure RotaTeq KD Case AN 94275

- 19 wks old (premature birth) Black Female, US
- Day 16 post dose 3
  - Vomiting , fever, rash, decreased appetite, IVIG and ASA 100 mg/kg begun for 2-3 weeks
  - Hospitalized for 6 days for iv fluids, CXR bronchial thickening, stool rotavirus RNA negative, CSF neg, Echo with pericardial effusion without coronary artery ectasia
- Day 32
  - Readmitted to hosp. for Kawasaki re-occurrence with URI symptoms, desquamation and erythema of palms and soles, no oral mucosa or conjunctival injection or strawberry tongue abnormalities, Echo with left coronary artery dilatation (no aneurysm) and systolic heart murmur noted, CXR and ECG WNL, repeat Echo 48 hours later reported to be WNL
- Followed by Peds Cardiology with normal echo and exam

Pre-licensure RotaTeq KD Case AN 97128

- 12 week old Hispanic-American Male
- Day 4 post dose 2
  - ER eval and received antibiotic
- Day 6 post dose 2
  - UTI and conjunctivitis
  - continued on antibiotic and Moxifloxacin added
- Day 7 post dose 2
  - Hospitalized as “fever rule out pyelonephritis”
  - Echo mild coarc, patent foramen ovale, “fine coronaries”, left to right shunt
  - Dx atypical Kawasaki and Rx high dose ASA x 5 days then low dose ASA x 8 wks.
- Day 39 post dose 3 follow-up Echo WNL
- Day 74 post dose 3 completed 8 wk course low dose ASA; recovered

Pre-licensure RotaTeq KD Case AN 39834

- 13 week old Black Male
- Day 27 Post dose 1
  - Fever, otitis media, erythromycin
- Day 29 Post dose 1
  - Temp to 104 F, cough, 3 day hx of chapped red bleeding lips and bulbar injection, palmar erythema, 3 day hx of truncal rash ; admitted and Rx for KD with IVIG and ASA, thrombocytosis
- Day 31 Post dose 1
  - Echo with widening of proximal right and left coronary arteries, discharged home on ASA 81 mg once daily

Pre-licensure RotaTeq KD Case AN 39855

- 22 week old White female
- Day 30 Post dose 3
  - 2 day hx Fever, conjunctivitis, strawberry tongue, irritability, leukocytosis and elevated platelets , KD diagnosed
- Day 34 Post dose 3
  - Continued fever and new rash and Rx with IVIG and ASA
  - Echo one dilated coronary artery
- Day 35 Post dose 3
  - Discharged home on aspirin (170 mg po q 6 hrs)
- Day 37 Post dose 3
  - KD resolved
- Day 40 Peds Cardiology notes symmetric dilatation of proximal left coronary artery but no aneurysmal dilatation
- 4.5 months later, repeat Peds Cardio eval with ECG and Echo are WNL

Pre-licensure RotaTeq KD Case AN 76738

- 19 week old White female
- Day 2 Post dose 2
  - Fever, Dx otitis media, Rx Zithromax
- Day 5 Post dose 2
  - Vomiting, diarrhea, conjunctivitis, red lips and oropharynx, puffiness, lacy rash on extremities, hospitalized, Rx IVIG and low dose ASA and Ceftriaxone, ranitidine, Echo and ECG WNL, blood cutures neg, later discharged after 7 days and doing well when seen 9 days after discharge

VAERS Case 1

- Two month-old female.
- From Hawaii, Korean ancestry from both parents
- Fever on day of multiple immunizations (DTaP, HIB, Hep B, IPV, PNC) including first dose Rotateq
- Generalized maculopapular rash (with question of possible reaction to iv ampicillin)
- Conjunctivitis (with yellow discharge)
- Dry and cracked lips, strawberry tongue
- No lymphadenopathy or swelling of hands and feet.
- The only echo change noted was pericardial effusion
- Treated with IVIG and aspirin
- Diagnosed as atypical Kawasaki by a known Kawasaki researcher (no coronary abnormalities reported)

VAERS Case 2

- Three month-old African American/Hispanic female
- From Texas
- Fever 2 days after multiple immunizations (including first dose RotaTeq), it lasted 5 days
- Generalized confluent rash
- Chapped red lips
- Conjunctival inflammation
- Edema of hands and feet
- Echo showed mild left coronary artery ectasia, AR, MR, and TR.
- Treated with IVIG and aspirin
- Case meets CDC case definition for Kawasaki

VAERS Case 3

- 6 1/2 month-old female from North Carolina
- Had multiple immunizations (including third dose RotaTeq)
- Had fever a few hours later that lasted 3 days
- Morbilliform rash on trunk that spread to limbs and face
- Edema of hands and feet
- Bilateral conjunctival injection
- Not clear whether or not pt had oropharyngeal erythema
- Also had emesis and diarrhea
- Concurrent “viral exanthem”, treated for otitis media
- No mention of echo findings or treatment with IVIG and aspirin for KD.
- Patient recovered

VAERS Case 4

- Received after FDA notification
- 5 month-old male from California
- Received multiple immunizations including second dose RotaTeq
- Pending investigation
  - Symptoms/treatment not described in report
  - Onset interval 14 days
  - Information has been requested

Merck RotaTeq® Post-licensure Safety Study (Protocol 019)*

- Ongoing, prospective observational safety study
- Large US health insurance plan population
  - Annual birth cohort ~100,000
  - Planned final study size: ~44,000 vaccinated children

*source: Merck unpublished data

FDA's June 15 Web Posting

Information Pertaining to Labeling Revision for RotaTeq®

Today, FDA approved a revised label for Merck's vaccine to prevent rotavirus infection, RotaTeq, to include information on Kawasaki disease. The Kawasaki disease finding is contained in the Biologics License Application (BLA). In addition, three reports of Kawasaki disease in children receiving routine pediatric vaccines, including RotaTeq, were detected through routine monitoring of the Vaccine Adverse Event Reporting System (VAERS). There is not a known cause and effect relationship between receiving RotaTeq, or any other vaccine and the occurrence of Kawasaki disease. The cases reported to date are not more frequent than what could be expected to occur by coincidence. Healthcare practitioners and parents should remain confident in using RotaTeq… ***(continues)***

* Source: http://www.fda.gov/cber/label/rotateqLBinfo.htm

CDC's June 15 Web Update

Kawasaki Disease and RotaTeq® Vaccine
Important Information Regarding Kawasaki Disease and RotaTeq Vaccine

The Food and Drug Administration (FDA) approved today a revised label for RotaTeq, a rotavirus vaccine manufactured by Merck and Co., Inc. (http://www.fda.gov/cber/products/rotateq.htm), to include information on reports of Kawasaki disease occurring before and after the vaccine's licensure in February 2006. FDA has not made any changes to its indications for use of RotaTeq nor has it issued new or revised warnings or precautions. Likewise, the Centers for Disease Control and Prevention (CDC) has not made any changes in its recommendations regarding the use of RotaTeq. Healthcare providers and parents should remain confident in using RotaTeq in infants.
….(continues)

http://www.cdc.gov/od/science/iso/concerns/kawasaki_disease_rotavirus.htm

Kawasaki Disease/Syndrome

- Uncommon childhood vasculitis of unknown etiology
- Occurs most frequently in Japan
- Disorder affects the mucus membranes, lymph nodes and blood vessels, including the coronaries
- Eighty percent of patients are younger than age 5 years.

RotaTeq® Pre-licensure Cases

- None in phase 1 and 2 clinical trials
- 6 cases from large phase 3 REST clinical trial
- None in smaller phase 3 studies 007 and 009
- Cases occurred in White, Hispanic and Black infants; in 3 male and 3 female infants; placebo case was Finnish
- Cases occurred after doses 1, 2 and 3
- Temporal Association
  - all within 2-30 days post-vaccination

Red Book® Diagnostic Criteria

- **Classic Disease**
  - **Fever for at least 5 days and at least 4 of the criteria listed below**
    - **Bulbar conjuctival injection without exudate**
    - **Erythematous mouth and pharynx, strawberry tongue, and red cracked lips**
    - **Polymorphous, generalized, erythematous rash (morbilliform, maculopapular, scarlatiniform or erythema multiforme**
    - **Changes in peripheral extremities e.g.induration of feet and hands with red palms and soles or periungual desquamation**
    - **Acute non-suppurative cervical adenopathy with one lymph node at 1.5 cm in diameter**
- **Non-classic or Incomplete**
  - **Febrile and less than 4 of the characteristic features**
  - **More common in infants < 12 months of age**
  - **Risk for cardiac complications**

Kawasaki Disease

- Treatment includes intravenous gamma globulin
- High-dose aspirin is often also given
- Even with treatment, 10-15% of children still develop coronary problems

Background on RotaTeq® Label change

- 5 Kawasaki cases among 36,150 RotaTeq recipients
  - 13.8 per 100,000 vaccinees
- 1 Kawasaki case among 35,536 placebo recipients
  - 2.8 per 100,000 vaccinees
- Unadjusted Relative Risk 4.92 (0.6-239.1)

- Approximately 20% of untreated children will develop coronary artery abnormalities
  - Infants who develop KD at higher risk for coronary artery abnormalities
  - “Incomplete KD” more common in infants
  - Importance of early recognition/intervention

Suspected Kawasaki Disease following RotaTeq® in VAERS*

Case #	Race Sex (State)	Age (months)	Dose	Interval (days)	Main Symptoms/signs	Treat-ment	Fits CDC KS case definition
1	Asian Female (HA)	2	1	0	Fever, rash, conjunctivitis. cracked lips	IVIG, aspirin	No
2	Black/ Hispanic (TX)	2	1	3	Rash, chapped red lips, conjunctival injection, edema of hands and feet, coronary ectasia	IVIG and aspirin	Yes
3	Female (NC)	61/2	3	0	Fever, rash, edema of hands and feet, Conjunctival injection	Unk	No
4	Male (CA)	5	2	14	Unk	Unk	No

* They all received multiple other childhood vaccinations on the same day, including DTaP, Hib, Hep B, Prevnar and IPV